REMARKS

The present response is believed fully to meet all of the objections and rejections set forth in Paper Nos. 5 and 6. The specification has been amended to correct obvious typographical errors and to comply with the requirements of 37 CFR §1.821(d) regarding the identification of sequences in a patent application. In particular, amendments to Table 3 on page 28 of the specification have been made to comply with the sequence identification requirements of 37 CFR §1.821(d). Support for the amendments to the specification inserting "SEQ ID NO" can be found by referring to the disclosed sequences preceding the site of insertion of the phrase "SEQ ID NO".

Claim 1 has been amended to further define the claimed invention. New claims 6, 7, and 8 have been added and are supported by the specification as filed (see, e.g., page 27, line 1 through page 32, line 1). In particular, the polypeptides listed in new claim 8 are set forth in Table 3 on page 28 of the specification, both as originally filed and as amended herein. Therefore, claims 1-8 are currently pending. Applicants believe that no new matter is presented by the within amendments.

In order to enhance clarity, Applicants will respond to the Office Actions in the order they were issued and received.

I. **Office Action mailed September 30, 1991 (Paper No. 5)**

A. Claims Free of Cited Art

First of all, the Applicants gratefully acknowledge the PTO's comment that Claims 2, 4, and 5 are free of the prior art.

B. The §112 Rejection

The PTO rejected claims 1-5 under 35 U.S.C. §112, first paragraph, for failure to provide an enabling disclosure. Applicants respectfully disagree with this rejection, for the following reasons.

First, Applicants urge that the "pulsating bubble" assay is

predictive of *in vivo* efficacy. In support of their position, Applicants submit herewith the Declaration of Dr. Charles G. Cochrane (hereinafter, "Cochrane Declaration") and the Declaration of Susan D. Revak (hereinafter, "Revak Declaration").

1. Demonstration of Superior Therapeutic Efficacy of the Claimed Peptides in Rhesus Monkeys

As shown in the Cochrane Declaration and Figures 1 through 4 attached thereto, the "pulsating bubble" assay results set forth and discussed in Example 2 on page 48, line 20 through page 55, line 11, and illustrated in Figure 6, were consistent with the *in vivo* data presented in the Cochrane Declaration. For example, Table 7 in the specification (see pages 53-54) shows that the pressure gradient of synthetic surfactant peptide RL4 was measured at 15 sec., 1 min., and 5 min., and was found to have mean values of 0.58, 0.65, and 0.33, respectively. As shown in Table 7, on page 54 of the specification, neither natural human surfactant nor phospholipid (PL) achieved the levels of surfactant activity exhibited by the synthetic surfactant peptides of the present invention, particularly RL4.

Just as the "pulsating bubble" assay was predictive of the *in vivo* therapeutic efficacy of various surfactant peptides as illustrated in Table 8 of the specification (see page 59, lines 6-60), that same *in vitro* assay is equally valid in predicting the therapeutic value of Applicants' synthetic surfactant peptides included in Table 3 of the specification (see page 28) as well as others encompassed by the formulations disclosed in the specification, including that set forth on page 27, lines 1-32 of the application. (See also Cochrane Declaration, para. 10.)

For example, in paragraphs 6-8 and Figures 1-2 of the Cochrane Declaration, the effect of administration to fetal Rhesus monkeys of RL4-containing surfactant on lung function is illustrated and discussed. In Figures 1 and 2, the data

generated by the administration of synthetic surfactant RL4 clearly illustrate that the index of oxygenation (a/A ratio) showed a striking increase subsequent to the administration of RL4. In other words, the administration of RL4-containing synthetic surfactant resolved the condition of severe respiratory distress in the monkeys and caused them to achieve normal breathing capacity within about 8-10 hours of administration of the synthetic surfactant.

In addition, dramatic results are seen when another synthetic peptide encompassed by the formulation of the present invention, i.e., synthetic peptide KL4 (Cochrane Declaration, para. 2) was administered in a blinded study using a population of fetal rhesus monkeys (Cochrane Declaration, para. 3). The four monkeys receiving KL4 ceased to exhibit signs of respiratory distress within a relatively brief period of time, usually about 6-10 hours after the administration of synthetic surfactant (Cochrane Declaration, para. 8 and Figs. 3A and 3B).

Even Monkey 8, which was suspected of having a septal defect (this was later confirmed on necropsy), gave indications of improved lung function on all parameters except a/A ratio (Cochrane Declaration, para. 8 and Fig. 3B). For example, the values for final oxygen in Monkey 8, as well as in the other 3 monkeys receiving KL4-containing surfactant, revealed that these animals tolerated low concentrations of inspired oxygen; their pCO_2 levels were low, final pH of their blood was normal, and their lungs were expanded as determined by gross and microscopic inspection (Cochrane Declaration, para. 8 and Figs. 3A and 3B).

Furthermore, in each of the eight cases illustrated in Figures 3A and B, X-rays performed immediately before surfactant administration demonstrated clouding of the lung fields, but only in the four monkeys receiving KL4-containing surfactant did the lung fields clear by 8-10 hours after birth (Cochrane Declaration, para. 4 and 8).

Clearly, then, the data support the conclusion that the synthetic surfactants containing a peptide conforming to the formulations disclosed in the above-referenced application are therapeutically useful, particularly in light of the observation that animals receiving these formulations fully recover from RDS after administration of a synthetic surfactant of the present invention (Cochrane Declaration, para. 9). In addition, the data indicate that administration of these novel peptide-containing surfactants allows recovery sufficient to warrant the removal of enriched oxygen administration once appropriate diagnostic parameters (e.g., the a/A ratio) indicate that the organism is no longer experiencing respiratory distress (Cochrane Declaration, para. 9).

Moreover, the experimental results obtained using the monkeys are consistent with, and predicted by, the information disclosed in the specification as filed (Cochrane Declaration, para. 10). In particular, the "pulsating bubble" assays described in the specification provide a valuable *in vitro* model of *in vivo* efficacy; the "bubble" assay results predicted that the synthetic surfactants of the present invention would demonstrate therapeutic efficacy, as illustrated herein (Cochrane Declaration, para. 10). In addition, the "bubble assay" results were consistent with, and predictive of, the therapeutic efficacy of various synthetic surfactants verified via the *in vivo* dynamic compliance assays described on pages 55-60 of the specification (Cochrane Declaration, para. 10).

2. Demonstration of Superior Therapeutic Efficacy of the Claimed Peptides in Fetal Rabbits

As shown in the Revak Declaration (and Tables 1-3 and Figure 1 attached thereto), the "pulsating bubble" assay results set forth and discussed in Example 2 on page 48, line 20 through page 55, line 11, and illustrated in Table 7 of the specification, were consistent with the *in vivo* data presented in the Revak

Declaration. Both sets of data confirm the therapeutic efficacy of the presently claimed peptides in mammals in general and present efficient models predictive of therapeutic efficacy in humans in particular.

For example, in paragraphs 5-9 and Tables 1-3 of the Revak Declaration, the effect of administration to fetal rabbits of RL2-, RL4- and RL8-containing surfactant on lung function is illustrated and discussed. In these Tables, the data generated by the administration of synthetic surfactants clearly illustrates the therapeutic value of these peptide-containing synthetic surfactants (Revak Declaration, para. 9). In Table 7 of the specification, the values generated via the "pulsating bubble" assay suggested that RL4 and RL8 would demonstrate a therapeutic effect *in vivo*; this suggested efficacy was borne out as predicted (Revak Declaration, para. 10-11 and Tables 1-3 attached thereto).

Figure A provides additional evidence of the predicted -- and demonstrated -- therapeutic efficacy of the synthetic surfactants of the present invention. Figure A illustrates *in vivo* dynamic compliance studies using synthetic surfactants $(RL4)_4R$, $(RL4)_5R$, $(RL4)_6R$, $(RL4)_7R$, and $(RL4)_8R$ (Revak Declaration, para. 6). This study further demonstrates that the synthetic surfactants of the present invention having alternating hydrophobic and hydrophilic amino acid residue regions and conforming to the disclosed formulations, have distinct therapeutic value (Revak Declaration, para. 8-11).

3. Discussion

Therefore, Applicants cannot agree with the PTO's conclusion that the *in vitro* data presented in the disclosure does not correlate with, or is not predictive of, efficacy of the claimed compositions *in vivo*. Applicants maintain that the specification as filed fully enables the claimed invention and demonstrates the therapeutic efficacy of the disclosed formulations.

As noted previously, *in vitro* tests can raise a presumption of *in vivo* usefulness of the claimed compositions. *Ex Parte Hirsch*, 34 PCTJ 588 (BOPAI 1987). Furthermore, recognized screening procedures which are interpreted by those skilled in the art as showing the disclosed pharmaceutical utility can be used to prove utility. *Ex parte Busse, et al.*, 1 USPQ2d 1908 (BOPAI 1988).

The PTO observed that the *in vivo* data presented in the specification (i.e., the lung compliance studies using fetal rabbits) were consistent with the *in vitro* data using the "pulsating bubble", but commented that *in vivo* data were not presented for the peptide species claimed in claim 18 or in claim 32 (which was abandoned in an earlier response). However, the PTO has presented no compelling arguments indicating why it believes the observed correlation between *in vitro* and *in vivo* data for the peptides listed in both Tables 7 and 8 of the specification would not be expected to apply to the peptide species of Claim 18 as well. Further, there is no evidence of record to suggest that the peptide species of Claim 18 would not work as claimed.

Whenever a rejection based on lack of enablement under 35 U.S.C. §112, first paragraph, is made, it is incumbent upon the PTO "to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement," *In re Marzocchi and Horton*, 169 USPQ 367, 370 (CCPA 1971). The PTO has presented no support or reasoning for its assertion that the correlation between the *in vitro* and *in vivo* studies applies for some, but not all, the peptides of the present invention.

Moreover, Applicants have presented evidence, both in the specification as filed and in the art, which support the use of the "pulsating bubble" assay as a reliable predictor of *in vivo*

efficacy of surfactant peptides. The efficacy of various synthetic surfactant polypeptides which was predicted by the disclosed *in vitro* studies was confirmed in the *in vivo* studies described in the Cochrane Declaration (see para. 7, in particular). Therefore, Applicants cannot agree with the PTO's apparent conclusion that the *in vitro* studies were valid predictors of efficacy for some, but not all, disclosed polypeptides.

As further evidence of the *in vivo* efficacy of the claimed polypeptides has now been presented, however, Applicants respectfully urge that the claims are now in condition for allowance.

C. The §103 Rejection

The PTO also rejected claims 1 and 3 under 35 USC §103 as being unpatentable over Jackson. Applicants respectfully disagree with this rejection as applied to the amended claims.

The PTO urges that a number of Applicants' peptides are encompassed by the generic disclosure of formula 1 of Jackson, but the PTO does not identify these peptides. Further, presuming for the sake of discussion that such an "overlap" exists between the two disclosures, the PTO has not established a sufficient rationale in support of its application of a §103 rejection against Applicants' specific formula.

To support a conclusion that a claimed combination is obvious, "either the references must expressly or impliedly suggest the claimed combination or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Int. 1985); see also *Ex parte Kranz*, 19 USPQ2d 1216, 1218 (Bd. Pat. App. & Int. 1991).

In the present instance, there does not appear to be a "claimed combination"; the PTO has rejected claims 1 and 3 in

view of a single reference. Moreover, the PTO has not indicated with what additional reference, if any, Jackson would be combined to suggest the presently claimed invention. As the Federal Circuit has stated, both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure. *In re Dow Chem. Co., supra.*

The PTO also has the burden of showing that the prior art would have taught or suggested the claimed invention to one of ordinary skill in the pertinent art. *In re Clinton*, 527 F.2d 1226, 1228, 188 USPQ 365, 367 (CCPA 1976). In addition, it is required that one of ordinary skill in the art would reasonably expect that the method suggested by the references would be successful. *Id.* Again, both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure. *In re Dow Chem. Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Thus, it is incumbent upon the PTO to show that the cited art would have suggested Applicants' formula to one of ordinary skill in the art.

The PTO must also present a "convincing line of reasoning" to support a rejection for obviousness. The PTO's line of reasoning seems to be based on a supposition that it would be obvious to one skilled in the art to ascertain the elegant, precise formulation of Applicants' invention on the basis of Jackson's rather unwieldy formula. This suggests little more than a variation of the "obvious to try" argument, which is certainly insufficient to constitute a "convincing line of reasoning."

Finally, a reference relied upon to support a rejection under 35 USC § 103 must itself be an enabling disclosure under 35 USC § 112, first paragraph. *In re Payne*, 203 USPQ 245, 255 (CCPA 1979). As discussed below, this single cited reference fails to enable the present invention.

The rejection premised upon Jackson reference does not meet

any of the above-enumerated criteria; moreover, the cited reference fails to expressly or impliedly suggest the claimed invention.

It is perhaps critical to an understanding of the tremendous difference between the disclosure of Jackson and that of the present invention to appreciate that Jackson's complex, largely unworkable formula fails to disclose or suggest the elegantly simple, symmetrical formulation disclosed by Applicants. Jackson's formulation specifies an amphipathic peptide -- specifically, a 21-mer polypeptide -- with one specific "outer area" (peptides A4, A5, A8, A9, A11, A12, A15, A16, A18, A19, A20) supposedly comprised of hydrophilic amino acids and another "outer area" (peptides A6, A10, A14, and A17). However, while Jackson sets these parameters for his 21-mer, he is inconsistent in the application of his own rules, utilizing amino acids in his specified hydrophilic or hydrophobic regions which clearly do not fit these designations.

There are other clear differences between the formula of Jackson and that of the Applicants. For example, formula 1 of Jackson is modeled on SP-A (which Jackson calls "apoA" -- see, e.g., column 1, lines 28-32). Conversely, the Applicants' formulation is modeled and based upon Applicants' analysis and characterization of SP-B, which has been shown in published studies to be the pulmonary surfactant protein most responsible for resistance to surface tension and prevention of collapse of pulmonary alveoli.

In addition, nowhere in the Jackson patent is there a description of the "Z_a" element in Applicants' polypeptides. Moreover, Jackson's formula does not disclose or suggest the significance of using hydrophobic rather than hydrophilic amino acid residues in the unambiguous manner disclosed by Applicants, nor does Jackson consistently recite which positions on his 21-mer are or are not hydrophobic.

Therefore, for all the above reasons, Jackson fails to disclose or suggest the specific formulation for Applicants' polypeptides and provides an inadequate basis for a §103 rejection.

D. The Provisional Double-Patenting Rejection

The PTO rejected claims 1-5 under the judicially-created doctrine of double patenting as being unpatentable over claims 17, 18, 31, 33, and 35-39 of copending application serial no. 07/293,201. The PTO further urges that the claims, albeit not identical, are not patentably distinct. Applicants respectfully disagree.

Nevertheless, once allowable subject matter is indicated by the PTO in the present case or in copending application serial no. 07/293,201, Applicants would be willing to file a terminal disclaimer if appropriate. To date, no claims have been allowed in either case.

E. The 37 CFR §§1.821-1.825 Objection

The PTO objected to the specification as failing to comply with the regulations regarding the submission of sequence data in a computer-readable format. Applicants' comments are as follows.

First, Applicants note that sequence data were not submitted as it was believed that the sequence data submitted in conjunction with copending application serial no. 07/293,201, of which the present application is a continuation-in-part, was sufficient to encompass the present disclosure. Nevertheless, it is now apparent that sequence data for three sequences shown in Table 3, namely, the KL4, KL7, and KL8 sequences, were not included in that earlier disclosure. Therefore, Applicants now submit sequence data herewith in full compliance with 37 CFR §§1.821-1.825. (See Declaration of April C. Logan enclosed herewith.) Therefore, Applicants submit that this objection is overcome and may now be withdrawn.

All matters raised in Paper No. 5 having been addressed,

Applicants urge that the claims are now in condition for allowance.

II. **Office Action mailed October 11, 1991 (Paper No. 6)**

A. Claims Free of Cited Art

The Applicants gratefully acknowledge the PTO's comment in Paper No. 6 that Claims 2-5 are free of the cited prior art.

B. The §102 and/or §103 Rejection

In the Supplemental Office Action (Paper No. 6), the PTO rejected Claim 1 under §102(a) or (b) as being anticipated by, or in the alternative, under §103, as being obvious over, the Ono et al. reference. In particular, the PTO urged that one peptide species falls within Applicants' generic claim; that species is cyclo(Leu-Lys-Leu-D-Leu-Leu)$_2$. The PTO based its urging on its presumption that the cyclic peptide would inherently have surfactant activity.

Applicants respectfully disagree with these rejections as applied to the amended claims. In particular, Applicants disagree with the PTO's presumption regarding the "inherent surfactant activity" of the cyclic peptide of Ono, et al.

The Court of Appeals for the Federal Circuit has repeatedly recognized that anticipation requires that **each and every element** of the claimed invention be disclosed in the prior art reference and that the prior art reference be enabling, thus placing allegedly disclosed matter in the possession of the public. (See, e.g., *Akzo N.V. v. U.S. International Trade Commission*, 808 F.2d 1471, 1 USPQ 2d 1241 (Federal Circuit 1986), *certiorari denied*, 107 S. Ct. 2470, 96 L. Ed. 2d 382.) The proper inquiry under 35 U.S.C. § 102 is whether a prior publication bears within its four corners adequate directions for practice of the patent invention. (See *Illinois Tool Works, Inc. v. Foster Grant Co., Inc.*, 395 F.Supp. 234 (D.C. Ill. 1974), affirmed 547 F.2d 1300, 192 USPQ 365, *certiorari denied*, 97 S.Ct. 2631, 53 L.Ed. 2d 243.)

The Ono et al. reference does not meet these criteria.

As the PTO correctly observes, there is no motivation provided by Ono et al. to prepare peptides greater than 10 residues in length which have stretches of Leu and Lys; neither does the reference suggest that these compositions can be used in the claimed methods. Accordingly, the PTO declared that all other claims of the instant application are free of this reference, which Applicant gratefully acknowledges.

However, while the PTO acknowledges that Ono, et al. does not suggest or disclose the use of its cyclic peptide as a synthetic pulmonary surfactant, it makes the contradictory argument that the synthetic pulmonary surfactant of claim 1 is either anticipated or rendered obvious in light of the cited reference, albeit there is clearly no evidence that the peptide of Ono, et al. would be useful for this purpose.

There is no support in the reference for the PTO's statements regarding "inherent surfactant activity" of the cyclic polypeptide. Moreover, the law regarding inherency is misapplied. As the Court of Customs and Patent Appeals observed, "the inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *In re Spormann*, 53 C.C.P.A. 1375, 150 USPQ 449, 363 F.2d 444 (1966). The PTO must establish that one of ordinary skill would anticipate success in the combination. *In re Rinehart*, 189 USPQ 143, 531 F.2d 1048 (C.C.P.A. 1976). Evidence of inherency is clearly lacking in the cited reference.

Notwithstanding Applicants' position that one cannot presume that Ono's peptide has inherent surfactant properties, Applicants have amended Claim 1 to recite that the polypeptide is <u>linear</u>, in an effort to expedite allowance of the claims. This amendment is supported by the specification as filed; see, e.g., page 11, lines 3-8, wherein the peptides of the present application are

described as comprising a linear series of residues. Therefore, it is respectfully submitted that this rejection may now be withdrawn.

The PTO is respectfully invited to telephone the Applicants at the number listed below if further discussion on this matter would be helpful, particularly in light of the fact that the PTO has indicated that claims 2-5 are free of the cited art. As claims 1 and 3 have now been amended to further clarify the invention, Applicants believe pending claims 1-7 are all in condition for allowance.

CONCLUSION

In view of the foregoing, it is submitted that patentable subject matter exists with regard to the claims as herein amended and favorable action in connection therewith is respectfully requested. Should any matters remain that might be resolved by telephone, the Examiner is courteously invited to contact the undersigned at the number given below.

Respectfully submitted,

Dated: 4-13-92 By: April C. Logan

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CERTIFICATE OF MAILING

I hereby certify that this AMENDMENT AND RESPONSE TO OFFICE ACTION UNDER 37 CFR §1.115 and the documents submitted therewith are being deposited with the United States Postal Service as first class mail, postage prepaid thereon, in an envelope addressed to: Hon. Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date indicated below.

4-13-92
Date

April C. Logan
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